REVIEW

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The Treatment Options for Generalized Pustular Psoriasis

Sera Nur Yücesoy, Burhan Engin

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology and Venereology, Istanbul, Turkey

ABSTRACT

Generalized pustular psoriasis is an uncommon variant of pustular psoriasis that includes many different treatment options. First line treatment options include acitretin, cyclosporine, methotrexate and infliximab. Besides these treatment options, there are many upcoming new molecules that are candidates for the treatment.

Keywords: Pustular psoriasis, Treatment, Immunosuppressant

Introduction

Generalized pustular psoriasis (GPP) is an uncommon variant of pustular psoriasis. The age of onset is usually within fifth decade. Although various medications and infections have a role in the disease process, the etiology is uncertain. The pregnancy form of the GPP is known as impetigo herpetiformis.

Multiple sterile pustules on erythematous skin are the most characteristic skin lesions. In addition, systemic symptoms including lymphadenopathy, fever, malaise can be seen in patients. There are many treatment options for GPP. First line treatment options include acitretin, cyclosporine, methotrexate and infliximab. Besides these treatment options, there are many upcoming new molecules that are candidates for the treatment.

Systemic retinoids are among the first line treatment of GPP. Acitretin is drug of choice for GPP and found to be effective in 85% of patients. It has the highest efficacy among first line treatment options. The optimal dosage for initial therapy is 0.75 to 1 mg/kg/day with the maintenance dose of 0.125 to 0.25 mg/kg/day [1]. Retinoids in general, should not be used in any patient who is pregnant or likely to become pregnant. Systemic retinoids may lead capillary leak syndrome in dose dependent manner [2]. Isotretinoin is inferior to acitretin in the treatment of GPP. It has shorter half life compared to acitretin [3]. Therefore, it is more suitable for the patients whose retinoid side effects are not desired.

Methotrexate is recommended for the patients with GPP who do not respond to systemic retinoids. It may take weeks to reach an effective dose since it has slow onset. The optimal dose for initial therapy is 5-15 mg/week with dose increment of 2.5 mg per week [4]. The most common side effects are gastrointestinal symptoms including diarrhea, nausea and vomiting. Periodic monitoring for complete blood test, liver and renal function tests is needed.

Cyclosporine, immunosuppressive calcineurin inhibitor, has rapid onset of action in GPP treatment. It is effective at doses of 2.5 to 5 mg/kg/day. Dose can be decreased gradually by 0.5 mg/kg every 2 weeks. The resolution of symptoms usually seen after 2 to 4 weeks [5].

Monoclonal antibodies have been approved for many inflammatory conditions in dermatology. Infliximab, anti-tumor necrosis factor (TNF) molecule, is highly effective and lead to dramatic improvement in GPP symptoms. The most of the studies supporting the use of infliximab in GPP are case reports [6,7,8]. It is known that the antichimeric antibodies to infliximab may decrease the

Address for Correspondence: Sera Nur Yücesoy MD, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology and Venereology, Istanbul, Turkey
Phone: +90 212 414 30 00 E-mail: syucesoy@ku.edu.tr ORCID ID: orcid.org/0000-0001-9170-4262
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effectiveness and increase the risk of transfusion reactions [9]. The addition of methotrexate to the treatment increases the efficacy of infliximab since methotrexate leads decrement in antibodies formed against infliximab [10]. The dosage of infliximab is 5 mg/kg at weeks 0, 2, 6 followed by maintenance dose every 8 weeks thereafter. Secukinumab is an anti-IL17A monoclonal antibody that can also be used in GPP treatment. Multiple case reports showed clinical improvement with secukinumab in GPP patients [11,12]. In one open-label study, clinical improvement was seen in 10 of 12 patients with GPP treated with secukinumab [13]. Ixekizumab, another anti-IL17A agent, may also be effective in the treatment of GPP patients. In an opel-label study with 78 GPP patients including plaque, erythrodermic and pustular psoriasis, 4 patients with GPP and 3 patients with GPP showed 75% and 90% clinical improvement respectively [14]. Brodalumab, anti-IL-17 monoclonal antibody, also lead clinical remission in GPP patients [15]. In addition to anti-IL17 molecules, guselkumab, directed against p19 subunit of IL-23, showed efficacy at week 16 in 7 of 10 patients with GPP [16]. Patients were treated with 50 mg guselkumab at weeks 0.4 and every 8 weeks thereafter.

Beside first line therapies, there are also other treatment options for GPP. PUVA photochemotherapy is among the second line therapies. It has slow onset of action, therefore usually considered for the patients whose acute symptoms were controlled. One of the disadvantages of PUVA photochemotherapy is the requirement of frequent clinical visits. In an uncontrolled study, PUVA 4 times/wk with mean 13.5 treatment session lead complete resolution of lesions [17].

As an TNF inhibitor adalimumab also showed clinical efficacy in some case control studies for GPP patients [18]. In one retrospective study, the symptoms of two-thirds of patients treated with adalimumab regressed in 4 week [19]. It should be noted that adalimumab can also trigger TNF-alpha induced pustular psoriasis. Therefore, careful monitoring is needed during adalimumab treatment.

Another biologic agent, ustekinumab has conflicting results in GPP treatment. In one case report, all 4 patients responded well to ustekinumab treatment. Three of four patients in this study were also taking low dose acitretin treatment. However, another case study reported flare of pustular psoriasis after ustekinumab treatment [20]. Therefore, the efficacy of ustekinumab treatment in GPP is debatable and further studies are needed to evaluate efficacy of ustekinumab in GPP treatment.

Anakinra, an interleukin (IL)-1 receptor antagonist, has shown clinical efficacy in GPP treatment in several case reports [21,22]. Canakinumab, another anti-IL-1-beta antagonist, may be also treatment option in GPP. In one case study, a patient with GPP responded well to anakinra treatment, developed hypersensitivity reaction to anakinra at the end of week 8. Therefore, the anakinra treatment was switched to canakinumab treatment. Patient received 150 mg subcutenous canakinumab injections every month over 1 year and the lesions resolved completely [23].

As for the novel drugs, anti-IL-36 receptor antagonists can also be used in GPP treatment since IL-36 is one of the main cytokines having a key role in pathophysiology of GPP. IL-36 is a member of proinflammatory cytokines that have a role in innate immunity. It was shown that mutations in IL-36R antagonist gene have been found in 40% to 80% of GPP cases [24]. Spesolimab, an anti IL-36R antibody, is a novel candidate for the treatment of GPP. In one study, 7 patients with the diagnosis of GPP had received single dose of 10 mg/kg spesolimab an followed for 20 weeks. Of those 7 patients, 3 patients had IL-36RN mutation and 1 patient had CARD14 mutation. At the end of week 4, all patients achieved efficacy endpoint GPP Physician Global Assessment GPPGA score of 0 or 1.

Mycophenolate mofetil (MMF), an inhibitor of inosine monophosphate dehydrogenase, is one of the widely used immunosuppressants. Several case reports support use of MMF in GPP [25,26]. Dapsone, 4,4'-diaminodiphenylsulfone, is anilin derived sulfone antibiotic which has anti-inflammatory and bacteriostatic effects. It inhibits neutrophil recruitment via inhibiting neutrophil myeloperoxidase and beta-2 integrin mediated adherence. Several case reports showed efficacy of dapsone in GPP treatment [27,28].

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.N.Y., B.E., Data Collection or Processing: S.N.Y., B.E., Analysis or Interpretation: S.N.Y., B.E., Literature Search: S.N.Y., B.E., Writing: S.N.Y.

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